CLAIMS

1. Use of peptide analogues of parent peptides, these parent peptides being derived, where applicable, from exogenous or endogenous proteins, the said parent peptides interacting with molecules of the MHC in the context of pathologies involving an immune response to cell mediation, in man or animals, the said analogues being characterized in that they correspond to the said parent peptides in which:

- at least one peptide bond -CO-NH- of the peptide chain is modified, with the exception of modifications of the retro or retro-inverso type, or
- at least one amino acid of the peptide chain is substituted with a non-protein-generating amino acid, or
- at least one peptide bond -CO-NH- of the peptide chain is modified and at least one amino acid of the said peptide chain is substituted with a non-protein-generating amino acid,

for the preparation of a medicinal product intended for preventing or treating the abovementioned pathologies.

2. Use according to Claim 1, of peptide analogues derived from parent peptides which interact with molecules of the MHC of category I, in the context of pathologies involving cytotoxic T lymphocytes.

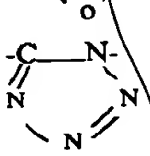
3. Use according to Claim 1 ~~or 2~~, of peptide analogues, characterized in that at least one of the peptide bonds -CO-NH- in the peptide chain of the parent peptide is replaced with a bond other than the -CO-NH-, the said other bond being chosen in particular from the following :

$-CH_2-NH-$	(methyleneamino) ;
$-CH_2-CH_2-$	(carba) ;
$-CO-CH_2-$	(ketomethylene) ;
$-CH_2-O-$	(methyleneoxy) ;
$-CHOH-CH_2-$	(hydroxyethylene) ;
-CH=CH-	(E or Z olefin) ;
-CHOH-CHOH-	(dihydroxyethylene) ;
-CHCN-NH-	(cyanomethyleneamino) ;
$-S-CH_2-$	(thiomethylene) ;
$-CH_2-S-$	(methylenethio) ;
-CS-NH-	(thioamide) ;
$-PO_2-NH-$	(phosphonamide) ;

-CHOH- (hydroxymethylene) ;

-NH-CO-NH- (urea) ;

-CH—CH- (oxirane) ;



(tetrazole) ;

$-CH_2-CO-NH-$ (β-homologation) ;

$-CHOH-CH_2-NH-$ (hydroxyethyleneamino) ;

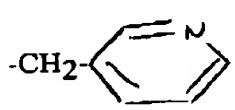
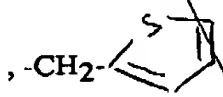
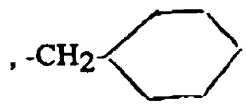
-CO-NH-NH- (hydrazino).

4. Use according to ~~one of Claims 1 to 3~~ claim 1, of peptide analogues, characterized in that at least one of the amino acids in the peptide chain of the parent peptide is substituted with a non-protein-generating amino acid, the said non-protein-generating amino acid being chosen in particular from the following amino acids:

- the amino acids of D configuration,
- the α-amino acids of the general formula:

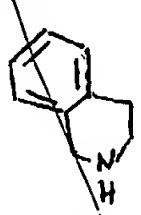
in which :

- R_1, R_2 and R_3, represent, independently of each other : a hydrogen atom, a hydroxyle, an alkyl radical of 1 to 25 carbon atoms, a radical containing an allyl group and having from 3 to 25 carbon atoms, a radical containing one or more aromatic or non-aromatic rings, in particular an aryl group, and having from 6 to 25 carbon atoms, and in particular the following groups: $-CH_3$ (methyl), $-CH_2CH_3$ (ethyl), $-(CH_2)_4-CH_3$, $-CH(CH_3)_2$ (isopropyl), $-C(CH_3)_3$ (tert-butyl), -Φ (phenyl), $-CH_2$ Φ (benzyl), $-CH_2$ ΦCl (para-chlorobenzyl), $-CH_2-CH_2$ Φ (2-phenylethyl), $-CH_2CHCH_2$ (alkyl), methylfluorenyl, $-CH_2CONH_2$ (glycolamide), $-CH_2CON\ \Phi_2$ (benzhydrylglycolamide), -CHOH Φ,

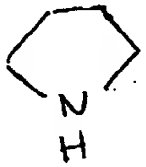




it being understood that one of the two groups R_2 and R_3 can represent a side chain of natural amino acids when either R_1 or the other of the two groups R_2 and R_3 do not represent a hydrogen atom,

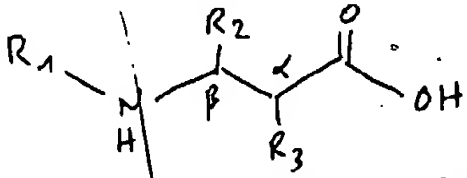
- where appropriate, R_1, R_2, Cα and N form an aromatic or non-aromatic heterocycle of 4 to 8 carbon atoms, which may be substituted, in particular a heterocycle of the formula :



or



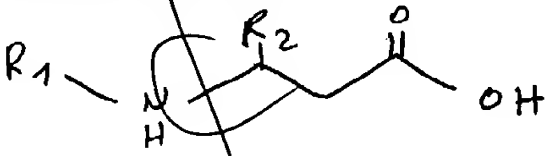
- the β-amino acids of the general formula :



in which R_1, R_2 and R_3, independently of each other, represent a side chain of a natural amino acid or are as defined above,

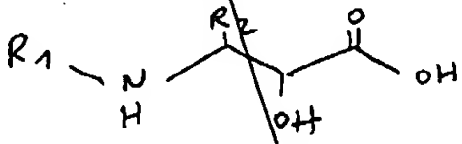
in particular :

. the β-homo amino acids of the formula:



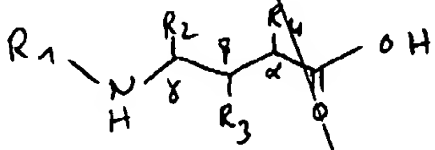
in which R_1 and R_2 are as defined above, or

. the α-hydroxy β-homo amino acids of the formula :



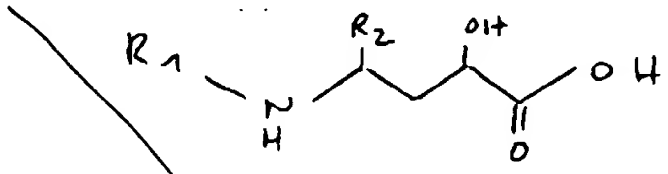
in which R_1 and R_2 are as defined above,

- the γ-amino acids of the general formula:



in which R_1, R_2, R_3 and R_4 represent, independently of each other, a side chain of a natural amino acid, or R_1, R_2 and R_3, are as defined above and R_4 has the same meaning as that given above for R_1, R_2 and R_3,

in particular the statin derivatives of the formula :



Claim 1

5. Use according to ~~one of Claims 1 to 4~~, of peptide analogues, characterized in that they are selected from those which are capable :

- on the one hand, of being recognized by the molecules of the MHC and of associating with these molecule, in particular by carrying out the following method :

. incubation of the peptide analogue in the presence of molecules of the MHC, derived from the lysis of human or animal cells, or purified in particular by affinity chromatography from human or animal cell lines, on a solid support coated with a first antibody, in particular a monoclonal antibody, which specifically recognizes the molecules of the MHC in their conformation which is dependent on their binding to the said peptide analogue

. addition to the above solid support of a second antibody which is labelled, in particular by means of coupling with a radioactive, enzymatic or fluorescent label, the said labelled antibody specifically recognizing either the molecules of the MHC in their conformation which is dependent on their binding to the peptide analogue, or a molecule which itself binds specifically to the molecules of the MHC in their abovementioned conformation, in particular β2-microglobulin which specifically recognizes the molecules of the MHC of category I,

. detection, after rinsing the solid support, of the possible presence of the second labelled antibody which has remained bound to the solid support, thereby demonstrating an effect of recognition and association between the molecules of the MHC and the peptide analogue studied,

- and, on the other hand, of forming a complex with the said molecules of the MHC, the stability of which complex can be evaluated by carrying out a method for monitoring over time the binding established between the peptide analogue and the molecules of the MHC, this method advantageously being carrying out according to a protocol which is identical to the above method, but in which the step of incubation of the peptide analogue in the presence of the molecules of the MHC on

the solid support coated with the said first antibody is carried out for times ranging from a few minutes to several days.

6. Use according to ~~one of Claims 1 to 5,~~ Claim 1, of peptide analogues, characterized in that they are selected :

* from those which are capable :

- of inducing *in vitro* the appearance and growth of cytotoxic T lymphocytes from human or animal cells, in particular from peripheral blood mononuclear cells (PBMCs) in the presence of factors required for the growth and differentiation of the cytotoxic T cells,
- of inducing *in vitro* cytolysis, by means of cytotoxic T lymphocytes, of target cells carrying at their surface the peptide analogue associated with the molecules of the MHC, the said cytotoxic T lymphocytes advantageously being taken from a patient suffering from a pathology in which the parent peptide of the peptide analogue studied is involved,
- and of inducing *in vitro* the secretion of cytokines (or interleukins) by means of the abovementioned cytotoxic T lymphocytes, in particular IL-2, IL-4 or γ-interferon,

the said peptide analogues thus selected being :

. either receptor agonists (TCR) which recognize the antigen (i.e. the parent peptide) of the cytotoxic T cells, and are derived from parent peptides which themselves behave as agonists or antagonists of the said receptors,

. or partial agonists of the said receptors, and are derived from parent peptides which themselves behave as agonists of the said receptors, these partial agonists inducing, in particular, the secretion of one or more cytokines other than those whose secretion is induced with the parent peptides,

* or from those :

- which are capable of inducing *in vitro* the appearance and growth of cytotoxic T lymphocytes from human or animal cells, in particular from peripheral blood mononuclear cells (PBMCs), in the presence of factors required for the growth and differentiation of cytotoxic T cells,
- which do not induce *in vitro* the cytolysis, by means of cytotoxic T lymphocytes, of target cells carrying at their surface the peptide analogue associated with the molecules of the MHC, the said cytotoxic T lymphocytes advantageously

being taken from a patient suffering from a pathology in which the parent peptide of the peptide analogue studied is involved,

- which do not induce *in vitro* the secretion of cytokines (or interleukins) by means of the abovementioned cytotoxic T lymphocytes, in particular IL-2, IL-4 or γ-interferon,

the said peptide analogues thus selected being antagonists of the cytotoxic T cell receptors.

7. Peptide analogues of parent peptides involved in melanoma, in particular the peptide MART1 27-35, the said parent peptide comprising, where appropriate, one or more mutations, such as the Leu^{28}-mutated parent peptide MART1 27-35, the said peptide analogues corresponding to the said parents peptides in which at least one of the peptide bonds -CO-NH- is modified, with the exception of modifications of the retro or retro-inverso type, the said analogues being chosen in particular from the following :

- the peptide analogues of MART1 27-35 in which at least one of the -CO-NH- bonds is replaced with a $-CH_2-NH-$ bond, such as the analogues Ψ(1-2) to Ψ(8-9) below :

Sequences

	P1	P2	P3	P4	P5	P6	P7	P8	P9
MART1 27-35	H –A -	A -	G -	I -	G -	I -	L -	T -	V -OH
Ψ (1 – 2)	H -A $\Psi_{(CH_2NH)}$	A -	G –	I -	G -	I -	L -	T -	V -OH
Ψ (2 - 3)	H –A - A	$\Psi_{(CH_2NH)}$	G -	I -	G -	I -	L -	T -	V -OH
Ψ (3 – 4)	H –A -	A - G	$\Psi_{(CH_2NH)}$	I -	G -	I -	L -	T -	V -OH
Ψ (4 - 5)	H –A -	A	G -	I	$\Psi_{(CH_2NH)}$ G -	I -	L -	T -	V -OH
Ψ (5 - 6)	H –A -	A	G -	I -	G	$\Psi_{(CH_2NH)}$ I -	L -	T -	V -OH
Ψ (6 - 7)	H –A -	A	G -	I -	G	I	$\Psi_{(CH_2NH)}$ L -	T -	V -OH
Ψ (7 - 8)	H –A -	A	G -	I -	G	I -	L	$\Psi_{(CH_2NH)}$ T -	V -OH
Ψ (8 - 9)	H –A -	A	G -	I -	G	I -	L -	T	$\Psi_{(CH_2NH)}$ V -OH

- the peptide analogues of MART1 27-35 in which at least one of the -CO-NH- bonds is replaced with a $-CH_2-CO-NH-$ bond, also referred to hereinbelow as a β-homo bond, such as the analogues β1 to β9 below :

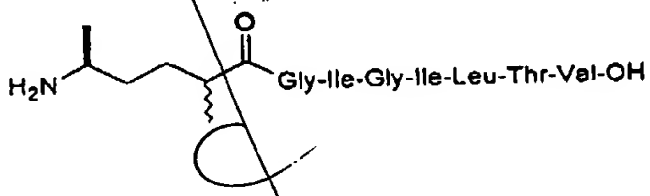
Sequences

	P1	P2	P3	P4	P5	P6	P7	P8	P9
MARTI 27-35	H –A	A -	G -	I -	G -	I -	L -	T -	V -OH
β1	H -β-homoA	–A -	G -	I -	G -	I -	L -	T -	V -OH
β2	H -A	–β-homoA -	G -	I -	G -	I -	L -	T -	V -OH
β3	H –A -	A -β-homoG -		I -	G -	I -	L -	T -	V -OH
β4	H –A -	A -	G -β-homoI -		G -	I -	L -	T -	V -OH
β5	H –A -	A -	G -	I -β-homoG -		I -	L -	T -	V -OH
β6	H –A -	A -	G -	I -	G -β-homoI -		L -	T -	V -OH
β7	H –A -	A -	G -	I -	G -	I -β-homoL -		T -	V -OH
β8	H –A -	A -	G -	I -	G -	I -	L -β-homoT -		V –OH
β9	H –A -	A -	G -	I -	G -	I -	L -	T -β-homoV	–OH

- the peptide analogues of MART1 27-35 Leu^{28} in which at least one of the -CO-NH- bonds is replaced with a $-CH_2$-CO-NH- bond, such as the abovementioned analogues β1 to β9 in which the alanine in P2 is replaced with a leucine,

- the peptide analogues of MART1 27-35 in which at least one of the -CO-NH- bonds is replaced with a $-CH_2-CH_2$- bond, such as the following analogues :

1



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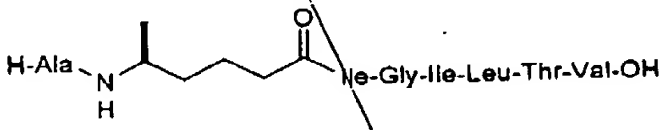
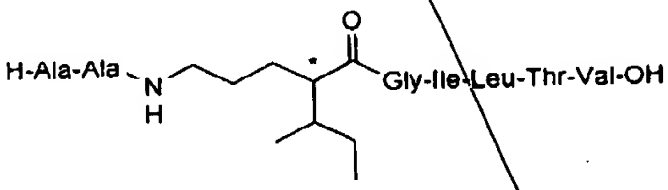
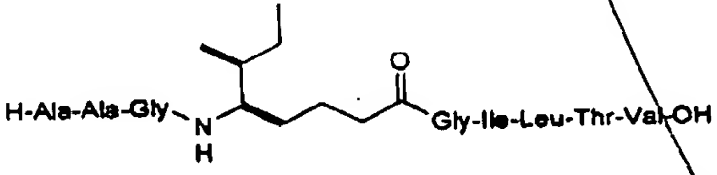
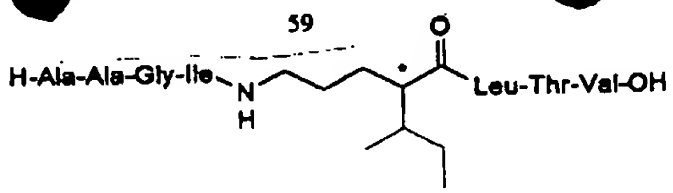


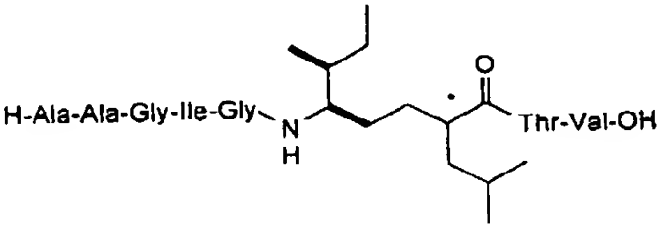
3

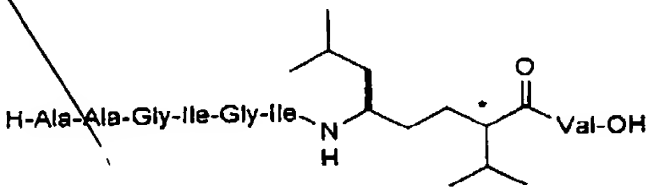


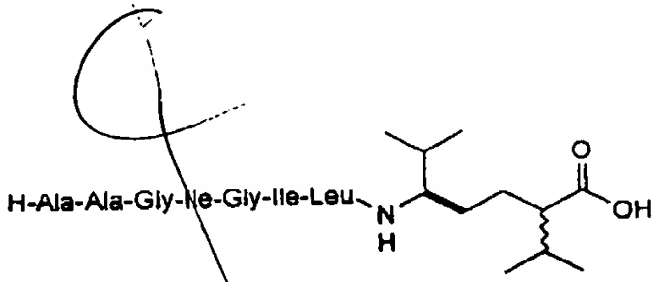
4











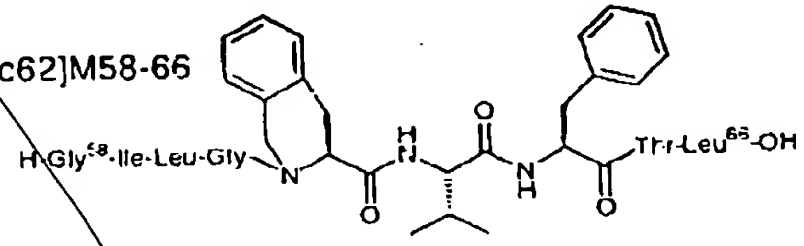
8. Peptide analogues of the parent peptides of the influenza virus, in particular of the parent peptide M58-66, the said peptide analogues corresponding to the said parent peptides in which:

- at least one of the -CO-NH- peptide bonds is modified, with the exception of modifications of the retro or retro-inverso type, the said analogues being chosen in particular from those in which at least one of the -CO-NH- bonds is replaced with a $-CH_2-NH-$ bond, such as the following analogues :

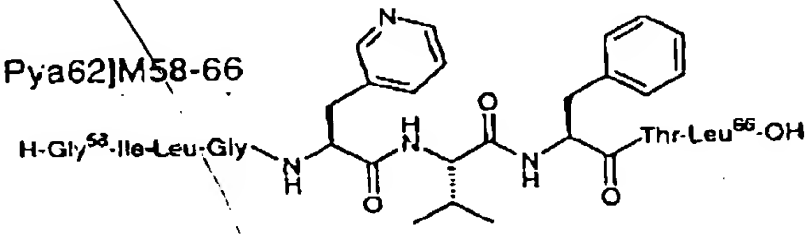
	Sequences P1 P2 P3 P4 P5 P6 P7 P8 P9
M58-66	H- G - L - L - G - F - V - F - T - L -OH
Ψ(1-2)	H-GΨ(CH_2NH)L-L - G - F - V - F - T - L -OH
Ψ(2-3)	H- G- LΨ(CH_2NH)L- G - F - V - F - T - L -OH
Ψ(3-4)	H- G - L -LΨ(CH_2NH)G- F - V - F - T - L -OH
Ψ(4-5)	H- G - L - L - GΨ(CH_2NH)F- V - F - T - L -OH
Ψ(5-6)	H- G - L - L - G - FΨ(CH_2NH)V- F - T - L -OH
Ψ(6-7)	H- G - L - L - G- F - VΨ(CH_2NH)F- T - L -OH
Ψ(7-8)	H- G - L - L - G - F - V - FΨ(CH_2NH)T - L -OH
Ψ(8-9)	H- G - L - L - G - F - V - F - TΨ(CH_2NH)L -OH

- at least one of the amino acids of the peptide chain is substituted with a non-protein-generating amino acid, such as the following analogues :

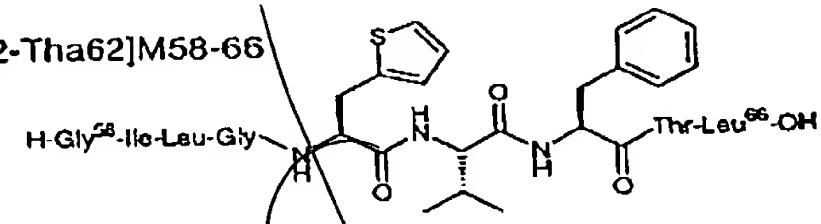
[Tic62]M58-66



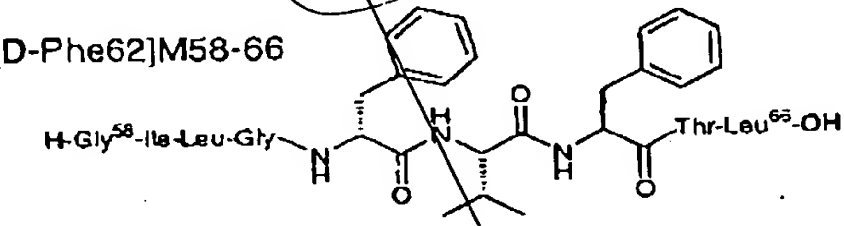
[3-Pya62]M58-66



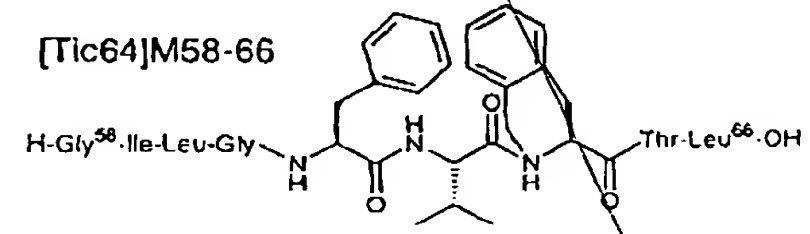
[2-Tha62]M58-66



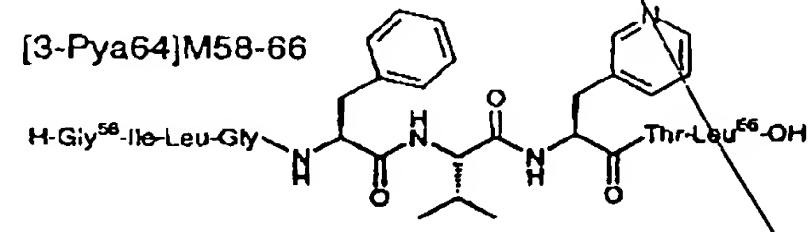
[D-Phe62]M58-66



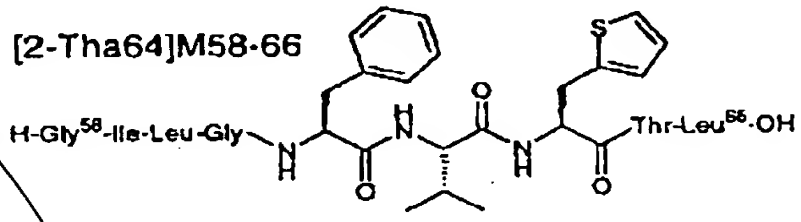
[Tic64]M58-66



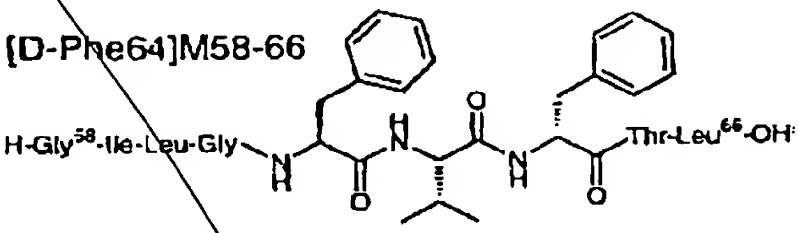
[3-Pya64]M58-66



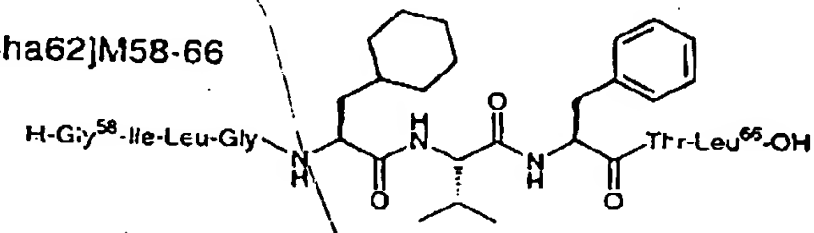
[2-Tha64]M58-66



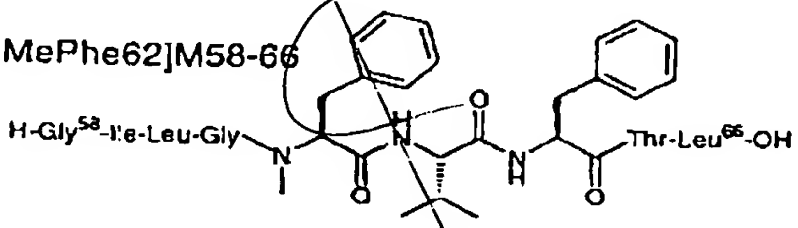
[D-Phe64]M58-66



[Cha62]M58-66



[N-MePhe62]M58-66



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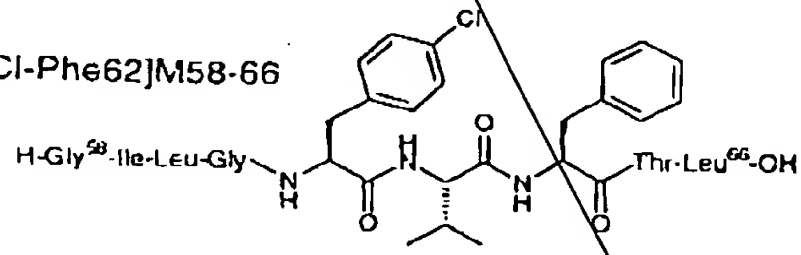

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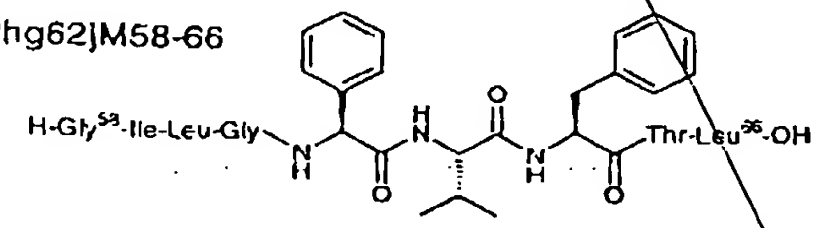

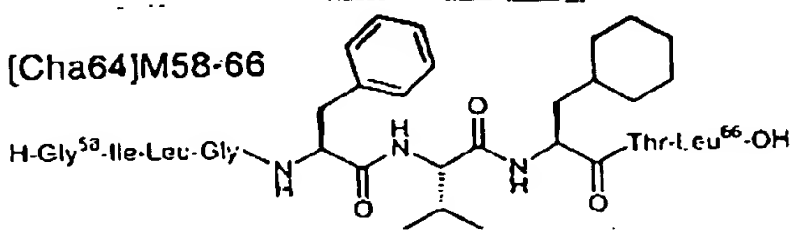

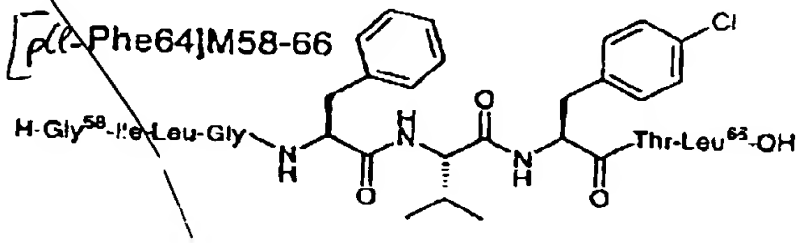

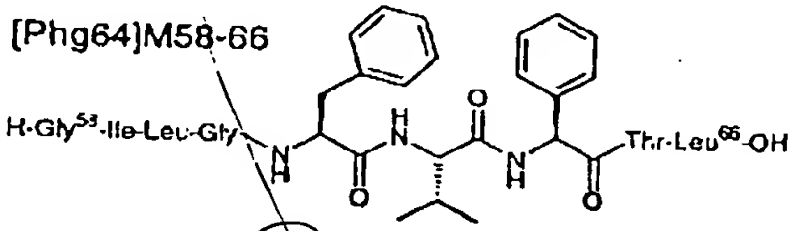

9. Peptide analogues of parent peptides of the AIDS virus, in particular of the peptides NEF 84-92 and GAG 77-85, the said peptide analogues corresponding to the said parent peptides in which at least one of the -CO-NH- peptide bonds is modified, with the exception of modifications of the retro or retro-inverso type, the said analogues being chosen in particular from :

- those in which at least one of the -CO-NH- bonds is replaced with a $-CH_2-NH-$, such as the analogues NEFRD1-8 of the peptide NEF, and GAGRD1-8 of the peptide GAG, below:

NEF	AVDLSHFLK
NEFRD1	AΨ(CH_2-NH)VDLSHFLK
NEFRD2	AVΨ(CH_2-NH)DLSHFLK
NEFRD3	AVDΨ(CH_2-NH)LSHFLK
NEFRD4	AVDLΨ(CH_2-NH)SHFLK
NEFRD5	AVDLSΨ(CH_2-NH)HFLK
NEFRD6	AVDLSHΨ(CH_2-NH)FLK
NEFRD7	AVDLSHFΨ(CH_2-NH)LK
NEFRD8	AVDLSHFLΨ(CH_2-NH)K

GAG	SLYNTVATL
GAGRD1	SΨ(CH$_2$-NH)LYNTVATL
GAGRD2	SLΨ(CH$_2$-NH)YNTVATL
GAGRD3	SLYΨ(CH$_2$-NH)NTVATL
GAGRD4	SLYNΨ(CH$_2$-NH)TVATL
GAGRD5	SLYNTΨ(CH$_2$-NH)VATL
GAGRD6	SLYNTVΨ(CH$_2$-NH)ATL
GAGRD7	SLYNTVAΨ(CH$_2$-NH)TL
GAGRD8	SLYNTVATΨ(CH$_2$-NH)L

- those in which at least one of the -CO-NH- bonds is replaced with a -CHOH-NH- bond, such as the following analogues NEFHEA1-8 of the peptide NEF:

NEF	AVDLSHFLK
NEFHEA1	AΨ(CHOH-NH)VDLSHFLK
NEFHEA2	AVΨ(CHOH-NH)DLSHFLK
NEFHEA3	AVDΨ(CHOH-NH)LSHFLK
NEFHEA4	AVDLΨ(CHOH-NH)SHFLK
NEFHEA5	AVDLSΨ(CHOH-NH)HFLK
NEFHEA6	AVDLSHΨ(CHOH-NH)FLK
NEFHEA7	AVDLSHFΨ(CHOH-NH)LK
NEFHEA8	AVDLSHFLΨ(CHOH-NH)K

10. Use of peptide analogues as defined in ~~one of Claims 1 to 9~~ Claim 1, for the preparation of medicinal products, in particular vaccines, intended for preventing or treating pathologies in which the parent peptides are agonists or antagonists of receptors which recognize the antigen of the cytotoxic T cells, and more particularly neurodegenerative pathologies which are infectious (of viral or bacterial origin), tumoural, autoimmune and allergic.

11. Pharmaceutical composition, characterized in that it comprises, as active principle, at least one peptide analogue defined in ~~one of Claims 1 to 9~~ Claim 1, in combination with a pharmaceutically acceptable vehicle.

12. Vaccine, characterized in that it comprises an agonist peptide analogue, which may be a partial agonist, defined in ~~one of Claims 1 to 9,~~ Claim 1 in combination with a pharmaceutically acceptable vehicle.

13. Diagnostic composition for the *in vivo* diagnosis of pathologies involving the immune response to cell mediation, in particular the cytotoxic T lymphocytes, or for the *in vivo* evaluation of the immune response in the context of the abovementioned pathologies, by carrying out a skin hypersensitivity reaction by means of intradermal injection of the said diagnostic composition, characterized in that it comprises a peptide analogue defined in ~~one of Claims 1 to 9,~~ Claim 1 in combination with a physiologically acceptable vehicle.

14. Complex between a peptide analogue defined in ~~one of Claims 1 to 9,~~ Claim 1, and a component of the major histocompatibility complex (also referred to as an MHC-peptide analogue binary complex), and optionally a T cell receptor (also referred to as an MHC-peptide analogue-T receptor ternary complex).

15. Method for the *in vitro* diagnosis of pathologies involving the immune response to cell mediation, in particular the cytotoxic T lymphocytes, i.e. pathologies associated with the presence, in a patient's body, of exogenous or endogenous peptides which interact with molecules of the MHC, and which are liable to be directly or indirectly involved in the process of development of these pathologies in man or animals, characterized in that it comprises:

- placing a biological sample, obtained from a patient, in contact with a peptide analogue defined in ~~one of Claims 1 to 9,~~ Claim 1, under conditions which allow reaction between the receptors of the T cells liable to be present in the biological sample, and the binary complex which may be formed between the said peptide analogue and the molecules of the MHC present in the said sample;
- the *in vitro* detection of the MHC-peptide analogue-T receptor ternary complex which may be formed in the preceding step.

16. Equipment or kit for carrying out ~~the~~ methods of *in vitro* diagnosis ~~according to Claim 15~~, comprising:

- a peptide analogue defined in ~~one of Claims 1 to 9,~~ Claim 1,

- reagents for making a medium suitable for forming an immunological reaction;

- reagents for detecting a ternary complex ~~according to Claim 14~~, which has been produced after the immunological reaction, the said reagents optionally containing a label or being capable of being recognized in turn by a labelled reagent, more particularly in the case in which the peptide analogue is not labelled.

17. Antibodies directed against the binary complexes as defined in Claim 14, the said antibodies being as obtained by immunizing an animal with at least one abovementioned binary complex, the said antibodies being capable of forming a complex with these binary complexes.

18. Pharmaceutical composition, characterized in that it comprises antibodies according to Claim 17, in combination with a physiologically acceptable vehicle.

19. Process for screening peptide analogues defined in claim 1, ~~one of Claims 1 to 9,~~ characterized in that it comprises the following steps :

. incubation for times ranging from a few minutes to several days, of the peptide analogue in the presence of molecules of the MHC, derived from the lysis of human or animal cells, or purified in particular by affinity chromatography from human or animal cell lines, on a solid support coated with a first antibody, in particular a monoclonal antibody, which specifically recognizes the molecules of the MHC in their conformation which is dependent on their binding to the said peptide analogue,

. addition to the preceding solid support of a second antibody which is labelled, in particular by means of coupling with a radioactive, enzymatic or fluorescent label, the said labelled antibody specifically recognizing either the molecules of the MHC in their conformation which is dependent on their binding to the peptide analogue, or a molecule which itself binds specifically to the molecules of the MHC in their abovementioned conformation, in particular β2-microglobulin which specifically recognizes the molecules of the MHC of category I,

. detection, after rinsing the solid support, of the possible presence of the second labelled antibody which has remained bound to the solid support,

. evaluation of the duration of the association between the said peptide analogue and the molecules of the MHC.

20. Set or kit for carrying out a screening process according to Claim 19, comprising:

- molecules of the MHC, and/or
- antibodies which specifically recognize the molecules of the MHC in their conformation which is dependent on their binding to the said peptide analogue, which antibodies are advantageously bound to a solid support, or are supplied with the reagents required for binding them to the solid support, and/or
- antibodies which are labelled, in particular by means of coupling with a radioactive, enzymatic or fluorescent label, this antibody specifically recognizing either the molecules of the MHC in their conformation which is dependent on their binding to the peptide analogue, or a molecule which itself binds specifically to the molecules of the MHC in their abovementioned conformation, in particular ###2-microglobulin which specifically recognizes the molecules of the MHC of category I, and/or
- a protocol for carrying out the said process, and/or
- a control peptide.

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